Copper-mediated S_N2' Allyl-Alkyl and Allyl-Boryl Couplings of Vinyl Cyclic Carbonates

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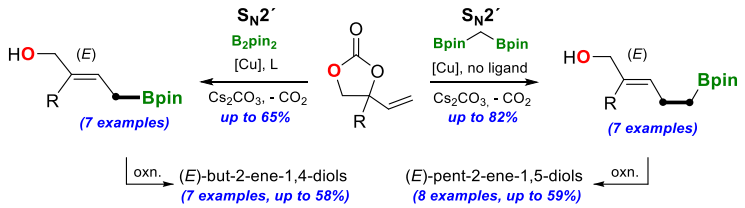
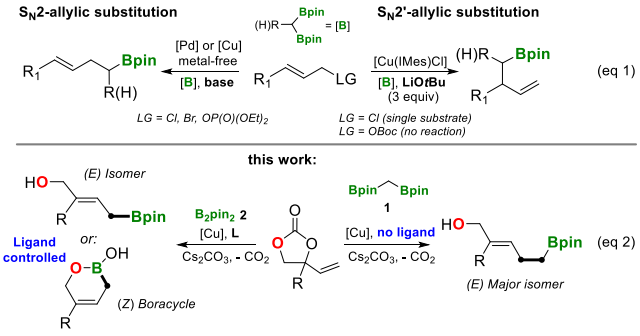


ABSTRACT: A method for the copper-catalyzed borylmethylation and borylation of vinyl cyclic carbonates through an S_N2' mechanism is reported. These singular reactions involve selective S_N2' allylic substitutions with concomitant ring opening of the cyclic carbonate, and with extrusion of CO_2 and formation of a useful hydroxyl functionality in a single step. The stereoselectivity of the homoallylic borylation and allylic borylation processes can be controlled, and synthetically useful unsaturated (*E*)-pent-2-ene-1,5-diols and (*E*)-but-2-ene-1,4-diols accessed.

Molecular diversity through organoboron chemistry provides easy-to-handle and shelf-stable materials that can be utilized in diverse transformations. The great potential of boron-selective reactions in simplifying experimental operations is due to the direct generation of C–B bonds formed from diboron reagents.[1] Alternatively, the use of 1,1-diborylalkane reagents to conduct nucleophilic borylmethylation has been less studied, despite the tremendous interest that homologated organoboron products offer as scaffolds in organic synthesis. *Gem*-diborylated compounds have shown to be useful reagents with alkyl-[2] and aryl-based electrophiles,[3] as well as with carbonyl compounds[4] mainly via base-induced deborylation. Diborylmethane reacts with allylic electrophiles to promote selective substitution reactions via S_N2 pathways under Pd/Cu catalysis or metal-free conditions (Scheme 1, top left).[5] However, to the best of our knowledge, there has only been one example related to the nucleophilic borylmethylation through an S_N2' mechanism, based on a copper-catalyzed selective allylic substitution of primary and secondary allylic chlorides with 1,1-diborylalkanes (Scheme 1, top right).[6a] Despite the usefulness of this approach, for substrates such as alkyl cinnamyl carbamates, the S_N2' allyl-alkyl coupling reaction proved to be unproductive.

Inspired by this limitation and in order to be able to extend the nucleophilic borylmethylation reaction through an S_N2' mechanism, we have explored copper (I)-catalyzed S_N2' allylic alkylation of vinyl cyclic carbonates with diborylmethane (**1**) (Scheme 1). This new approach would allow additional functionality to be retained in the homoallylic borylated product since a hydroxyl group is generated with the concomitant loss of CO_2, providing access to scaffolds that are not easily prepared through other routes. For the sake of comparison, the copper(I)-catalyzed S_N2' allylic borylation of the same allylic cyclic carbonates with B_2pin_2 **2** has also been studied and control over the stereoselectivity of the allylic borylated product was explored since both *E* to *Z* isomers can be formed. Stereoselective synthesis of allylboronates with a hydroxyl terminus would potentially provide an unprecedented route towards functionalized allylboronates.[7]

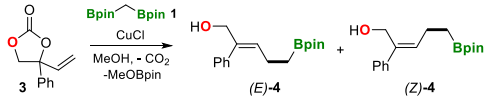
Scheme 1. Allyl-Alkyl Couplings using Allylic Electrophiles and *Gem*-Diborylated Compounds (eq 1), and New Allyl-Alkyl or Allyl-Boryl Couplings using Vinyl Cyclic Carbonates and Diborylmethane or B_2pin_2 (eq 2)



Initially we carried out the reaction between the vinyl cyclic carbonate **3** and diborylmethane **1** in the presence of MeOH as solvent and base to *in situ* generate the Cu-OMe derivative from CuCl (Table 1). The estimated copper salt loading and ligand (where required) was 9 and 13 mol %, respectively. At rt, substrate **3** (0.2 mmol scale) reacted with reagent **1** (1.2 equiv) providing moderate conversions of the desired homoallylic borylated product (*E*)-(5-hydroxy-4-phenylpent-3-en-1-yl)boronate ester **4** mediated by CuCl/SIPr or CuCl/PPh_3 (Table 1, entries 1 and 2). The exclusive formation of the new C–C bond at the terminal position exemplifies the regiocontrol of the allyl-alkyl cross-coupling reaction, but of particular note is that the S_N2' process allows for simple extrusion of CO_2 from the

cyclic carbonate precursor, keeping a synthetically useful OH functionality. In the absence of any ligand, the unmodified copper species generated product (*E*)-**4** in up to 58% yield (Table 1, entry 3). Neither the use of a double amount of diborylmethane nor the presence of alternative bases such as LiO*t*Bu improved the reaction outcome (Table 1, entries 4 and 5). A higher Cs_2CO_3 loading (50 mol %) was optimal to achieve quantitative conversion and **4** was obtained in a yield of 75% (*E*/*Z* = 4:1) (Table 1, entry 6). Interestingly, the ratio of *E*/*Z* stereoisomers is higher than the *E*/*Z* ratios observed in the cross-coupling of vinyl cyclic carbonates with arylboronic acids catalyzed by Pd nanoparticles.[6b]

Table 1. Allyl-Alkyl Couplings between Diborylmethane and the Vinyl Cyclic Carbonate 3.[a]



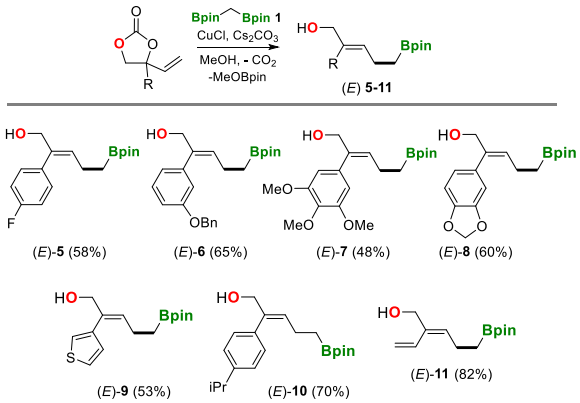
entry	Cu/ligand	base (mol %)	*E*/*Z*	yield (*E*)[b]
1	CuCl/SIPr	Cs_2CO_3, 15	3.9:1	35
2	CuCl/PPh_3	Cs_2CO_3, 15	4:1	13
3	CuCl	Cs_2CO_3, 15	4:1	58
4[c]	CuCl	Cs_2CO_3, 15	4:1	40
5	CuCl	*t*-OBuLi, 15	4:1	24
6	CuCl	Cs_2CO_3, 50	4:1	75

[a]Conditions: carbonate (0.2 mmol), $CH_2(Bpin)_2$ (1.2 equiv), CuCl (9 mol %), ligand (13 mol %), Cs_2CO_3 (50 mol %), MeOH (0.10 mL), rt, 16 h. [b]NMR yield using naphthalene as internal standard. [c]$CH_2(Bpin)_2$ (2 equiv).

Since the only examples known for copper-catalyzed S_N2'-selective allylic substitution reaction between 1,1-diborylalkanes and allylic chlorides[6a] were unproductive for allylic acylic carbonates, the newly developed protocol (Table 1) provides complementary reactivity. In addition, no sign of S_N2-substitution could be detected and the proposed copper-catalyzed S_N2'-selective allylic substitution thus represents a carbonate ring opening reaction under relatively high stereocontrol.

We next explored the allyl-alkyl coupling of a series of substituted vinyl cyclic carbonates and diborylmethane to further expand this Cu-catalyzed process (Scheme 2) (conditions: Table 1, entry 6). A general trend is observed in the formation of the borylated products **5–11** with the *E* isomer being the favored stereoisomer. In all crude reaction products, the *E*/*Z* ratios were close to 4:1 independent from the substituent present in the vinyl cyclic carbonates. Both stereoisomers could be isolated from the reaction media; the corresponding isolated yields of the *E* isomer are shown in Scheme 2 (Supporting Information, SI, for details on the *Z*-isomers). Electron-donating or -withdrawing substituents in the aryl group (as well as their relative position) did not interfere in the formation of the homoallyl boronates (*E*)-**5**, (*E*)-**6**, (*E*)-**7**, (*E*)-**8** and (*E*)-**10**, with yields of up to 70%. The reaction is also tolerant towards other functionalities present in the vinyl cyclic carbonate substrate, including thiophenyl groups (*cf* (*E*)-**9**), and an interesting butadiene derivative (*E*)-**11**, which was isolated in high yield (82%).

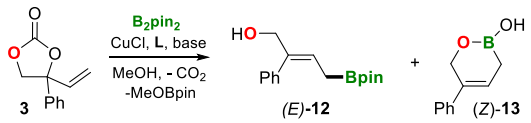
Scheme 2. Substrate Scope for the Allyl-Alkyl Couplings between Diborylmethane and Vinyl Cyclic Carbonates.



To further test the viability of the C–B bond formation from vinyl cyclic carbonates, we carried out the reaction between substrate **3** and B_2pin_2 **2** in the presence of MeOH as solvent and base (Table 2). When CuCl (9 mol %) was used (Table 2, entry 1), the conversion of **3** was quantitative with the principal formation of the allyl boronate (*E*)-**12** (isolated yield 60%) together with a minor amount of a secondary product. Interestingly, the latter was isolated as a result of an *in situ* intramolecular cyclization process from the *Z* stereoisomer. The nucleophilic attack of the boryl moiety onto the vinyl cyclic carbonate **3** readily takes place at rt through a "Cu-Bpin" intermediate that is formed *in situ* from a CuCl/MeOH/base/B_2pin_2 combination.[8] Notably, the transition-metal free version does not allow for the allylic borylation of vinyl cyclic carbonates.[9]

The copper catalyzed reaction proceeds regioselectively as the C–B bond was exclusively formed at the terminal position of the allylic intermediate confirming the S_N2' mechanism.[10] In the absence of any ligand, the formation of some degraded substrate could be observed (Table 2, entry 1), and the use of alternative bases such as *t*-OBuK in the allylic borylation of **3** reduced both the overall conversion and stereoselectivity (entry 2). We also carried out a reaction with a preformed CuO*t*-Bu catalyst (entry 3)[11] and found that it worked comparably to the *in situ* formed catalyst derived from CuCl/*t*-OBuK in MeOH. Therefore, we continued with the *in situ* prepared catalyst in the presence of B_2pin_2. The amount of base was optimized to 15 mol %, which is significantly less than the amount of base used in similar copper-catalyzed allylic borylations requiring typically 1–3 equiv. The use of an *N*-heterocyclic carbene ligand slightly modified the reaction outcome in the allylic borylation of **3** since the process was more efficient in terms of total conversion towards the borylated products (entry 4). In the presence of SIPr, the formation of the allylboronate (*E*)-**12** also gave an improved yield of 69%. A CuCl/PPh_3 based catalyst gave a mixture of borylated compounds **12** with an *E*/*Z* ratio of 57:35 (Table 2, entry 5). The use of bidentate phosphine ligands, however, favors the formation of boracycle (*Z*)-**13**. An improved selectivity towards (*Z*)-**13** was achieved when the diphosphine 1,2-bis(diphenylphosphino)ethane (dppe) was used, giving an *E*/*Z* ratio of 36:52 (Table 2, entry 6). Interestingly, when the diphosphine 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (PP) was added, exclusive formation of boracycle (*Z*)-**13** could be achieved (Table 2, entry 7).

Table 2. Allyl-Boryl Couplings between B_2pin_2 and the Vinyl Cyclic Carbonate 3.[a]

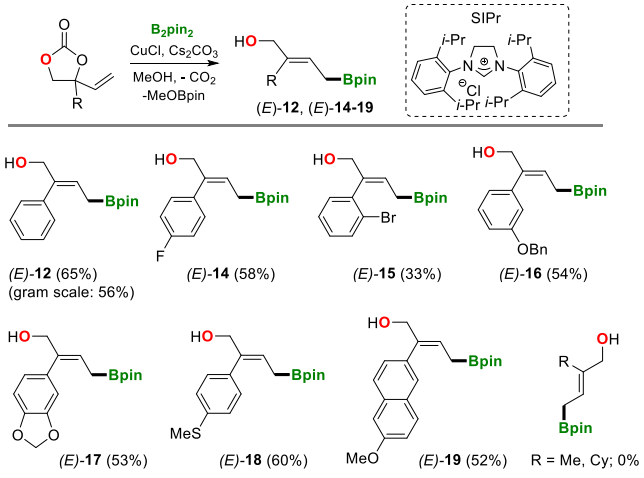


entry	Cu/ligand	base	conv[b] (%)	(*E*)-**13** (%)[b]	(*Z*)-**13** (%)[b]
1	CuCl/–	Cs_2CO_3	95 [c]	62 (60)	17
2	CuCl/–	KO*t*Bu	61	41 (40)	19
3	CuO*t*Bu/–	Cs_2CO_3	64	47 (37)	15
4	CuCl/SIPr	Cs_2CO_3	99	69 (65)	31 (30)
5	CuCl/PPh_3	Cs_2CO_3	99	57	35
6	CuCl/dppe	Cs_2CO_3	91	36 (24)	52 (39)
7	CuCl/PP	Cs_2CO_3	99	–	72 (45)

[a]Conditions: carbonate (0.2 mmol), B_2pin_2 (1.2 equiv), Cu salt (9 mol %), ligand (13 mol %), Cs_2CO_3 (15 mol %), MeOH (0.10 mL), rt, 16 h. A high throughput screening of ligands can be found in the SI. [b]Calculated by ^{1}H NMR ($CDCl_3$) using mesitylene as internal standard. Values in brackets represent isolated yields. [c] <5% degraded substrate was observed.

While copper-mediated decarboxylative allylic borylation reactions of acyclic carbonates have been used to obtain allenylboronates,[12,13] vinylboronates[14] and allylboronates,[15] those methods lose the whole OCO_2R functional group during the C–B bond formation. Our method permits additional functionality to be retained in the final product. Taking advantage of this new methodology, we explored the borylation of a series of vinyl cyclic carbonates using CuCl/SIPr as the catalyst system (conditions: Table 2, entry 4) to give the (*E*)-allylboronates **12** and **14**–**19** as the main product (Scheme 3). The conversion of different carbonate precursors into their borylated products was almost quantitative in most cases, with some minor amount of the (*Z*)-isomers being formed (<10%) together with some degraded substrate. In general, rather similar isolated yields were obtained (52–65%) independent from the type of substrate. The borylation of **3** could also be carried out on gram scale in a slightly lower yield (56%, Scheme 3), but the use of vinyl carbonates with alkyl groups (R = Me, Cy) was unproductive.

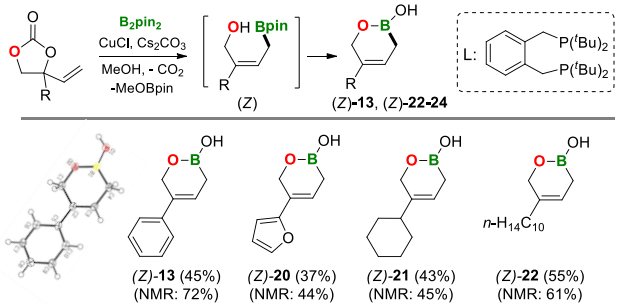
Scheme 3. (*E*)-Selective Allyl-Boryl Couplings between B_2pin_2 and Vinyl Cyclic Carbonates.



When 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (PP) was used as ligand, the allylic borylation of alkyl/aryl-substituted vinyl cyclic carbonates advanced towards the (*Z*)-stereoisomer following intramolecular cyclization to afford the boracycles **13** and **20–22** (Scheme 4) (conditions: Table 2, entry 7).

(*Z*)-Boracycles are important in the context of diversity-oriented organic synthesis,[16] as well as in organoboron based drug discovery.[17] Other boracycles have exclusively been obtained through our copper-catalyzed borylation to allylic cyclic carbonates, but the isolated yields were relatively low (see SI for details). The molecular structure of (*Z*)-**13** was also confirmed by X-ray diffraction (Scheme 4, inset).

Scheme 4. (*Z*)-Selective Allyl-Boryl Couplings between B_2pin_2 and Vinyl Cyclic Carbonates.



A proposed reaction mechanism for the S_N2' allyl-alkyl coupling (Figure 1 and SI for further details) and S_N2' allyl-boryl coupling reactions may involve first activation of the diborylmethane reagent or B_2pin_2 to form Cu-CH_2Bpin or Cu-Bpin, respectively. Figure 1 shows that Cu-CH_2Bpin intermediate **A** coordinates the terminal alkene of substrate to generate **B** followed by regioselective addition producing a new alkyl-Cu intermediate **C**. Hereafter, elimination of the product from **D** in a formal *anti*-S_N2' pathway releases CO_2 and regenerates the copper complex.

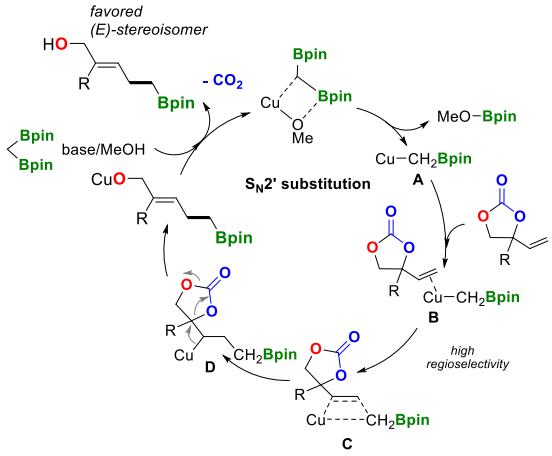
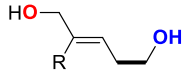
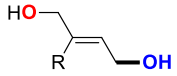


Figure 1. Proposed Mechanism for S_N2' Allyl-Alkyl Coupling

To demonstrate the synthetic use of the homoallylic and allylic borylated products, we conducted an *in situ* copper-catalyzed S_N2' allyl-alkyl and S_N2' allyl-boryl coupling followed by oxidative work up (H_2O_2, NaOH). The corresponding (*E*)-configured pent-2-ene-1,5-diols and but-2-ene-1,4-diols were isolated as the main products (Figure 2). The corresponding (*Z*)-isomers of the pent-2-ene-1,5-diols could also be isolated in low yield (see the SI). Interestingly, the (*E*)-isomers of such but-2-ene-1,4-diols are valuable compounds, being about 190 times more expensive than their corresponding (*Z*)-isomers.[18] Therefore, our versatile one-pot approach opens a new straightforward route towards these scaffolds[19] which are useful in organic synthesis.[20]



(*E*)-**23** R = Ph, (47%)
(*E*)-**24** R = *p*-F-C_6H_4, (41%)
(*E*)-**25** R = *m*-BnO-C_6H_4, (59%)
(*E*)-**26** R = 3,4,5-tri-MeO-C_6H_2, (45%)
(*E*)-**27** R = benzo[*d*][1,3]dioxole, (55%)
(*E*)-**28** R = 3-thiophenyl, (27%)
(*E*)-**29** R = *p*-iPr-C_6H_4, (47%)
(*E*)-**30** R = vinyl, (32%)



(*E*)-**31** R = Ph, (52%)
(*E*)-**32** R = *p*-F-C_6H_4, (47%)
(*E*)-**33** R = *m*-BnO-C_6H_4, (54%)
(*E*)-**34** R = 3,4,5-tri-MeO-C_6H_2, (45%)
(*E*)-**35** R = benzo[*d*][1,3]dioxole, (42%)
(*E*)-**36** R = *p*-MeS-C_6H_4, (58%)
(*E*)-**37** R = 2-(6-MeO-naphthyl), (47%)

Figure 2. One-Pot Preparation of But-2-ene-1,4-Diols and Pent-2-Ene-1,5-Diols

In conclusion, we present a stereoselective copper-catalyzed selective S_N2' allylic substitutions of vinyl cyclic carbonate to form allylboranes and homoallylboranes. The stereoselectivity is catalyst-controlled and *in situ* copper-catalyzed C–CH_2B and C–B bond formation followed by oxidative workup provides direct access to valuable (*E*)-configured pent-2-ene-1,5-diols and but-2-ene-1,4-diols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information contains experimental procedures and characterization of all allyl-alkyl couplings using vinyl cyclic carbonates and diborylmethane or B_2pin_2. It is available free of charge on the ACS Publications website at DOI: 10.1021/XXX

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Author Contributions

The manuscript was written through contributions of all authors.

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